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# *In-Silico* Analysis Of Phytoconstituents As Potential Cox-2 Inhibitors For Rheumatoid Arthritis Therapy

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**Abstract**

**Rheumatoid Arthritis (RA) is a long-term autoimmune disease which is associated to the perennial inflammation in the joints which is catalyzed by enzymes such as COX-2. This research work was conducted with the aim of assessing the presumable anti-arthritic effects of six phytoconstituents, namely, EGCG, Boswellic acid, Withaferin A, Piperine, 6- Gingerol, and Harmine via molecular docking against the COX- 2 protein (PDB ID: 5F19). Diclofenac sodium was taken as a reference. Docking was carried out in Molegro Virtual Docker and the analysis based on MolDock scores of success as well as hydrogen bond interaction. EGCG in Camellia sinensis had the highest affinity (-148.025 MolDock score), then Boswellic acid and Withaferin A that was better than the standard drug. These newer observations indicate that the plant derived materials and particularly EGCG can be an effective and safer COX-2 inhibitor in the treatment of RA. These computational insights ought to be further validated in experiment.**

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**Keywords:** Cyclooxygenase-2 (COX-2), Molecular Docking, Phytoconstituents, Rheumatoid Arthritis, Epigallocatechin-3-gallate (EGCG)

## INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic autoimmune disease which achieves its most active manifestations in synovial joints causing the destruction of cartilage and bones. RA affects a population of about 0.5-1 percent globally, and women develop this problem more than men in a ratio of 3:1. RA development is closely associated with the phenomenon of autoimmune responses, which have a genetic, epigenetic, and environmental background. The development of the RA may be divided into three steps, including the first stage, when the swelling and pain occur, the second when the synovium becomes inflamed, and the third step when the bone and the cartilage are destroyed to bring constantly painful joints and legs. Some of the pro-inflammatory cytokines, such as, Interleukin-1B, Interleukin-17, Interleukin-34, IL 17 and Tumor Necrosis Factor-alpha (TNF-alpha) and enzymes such as Cyclooxygenase-II (COX-II), Lysyl Oxidase (LOX) Anti prostaglandin- gamma synthase (PTGS), Reactive Oxygen Species (ROS) such as Nitric Oxide (NO) and of all these, COX-II, PTGS, and LOX have been singled out as targets of the RA treatment, especially when it is chronic [1-10].

Existing modalities of the treatment of RA comprise standard pharmaceuticals including steroidal drugs (corticosteroids), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including ibuprofen and naproxen, as well as Disease-Modifying Anti-Rheumatic Drugs (DMARDs) which include methotrexate and leflunomide. RA is also controlled with biological therapies such as TNF- o alpha blockers (rituximab), anti CD 20 blockers (rituximab), and abatacept. These drugs assist with reducing swellings and giving relief but they are only short-term beneficial and usually come with severe side effects. The classic DMARDs like the methotrexate are linked with such adverse reactions as nausea, vomiting, kidney dysfunction and hematological problems such as anemia and thrombocytopenia [11-17].

Since synthetic medicines are accompanied by side effects, there is an alternative, that is herbal or natural medicines, which have minimal side effects. In India, more than 2,500 plant species have been used as the source of traditional medicine to treat diseases, such as RA. Most of these vegetable treatments are strong antioxidants, and have the ability to hunt down free radicals that also cause inflammation and cartilage breakdown in rheumatoid arthritis. Phytochemicals contained in such plants are able to bind and regulate the expression of pro-inflammatory signals, something that eventually eliminates the deleterious impacts of arthritis. Going further, the anti-arthritic effect against COX-II has become an area of interest due to the fact that COX-II inhibitors have the ability of lowering down the concentration of pro-inflammatory prostaglandins that are known to be of significant effect in arthritis development and perpetuation. These inhibitors are regarded as a potential treatment option in chronic inflammation in RA, and it has a lower chance of gastrointestinal complications than conventional NSAIDs [18-24].

### *Boswellia serrata*

Indian frankincense or *Boswellia serrata* is a well-researched agent with its strong anti-inflammatory and anti-arthritic effects. Active components found in Boswellia especially through boswellic acids result in the prevention of the production of pro-inflammatory cytokines and enzymes like cyclooxygenase-2 (COX-2) and therefore suppress inflammation and pain related to arthritis. It has depicted effectiveness in alleviating symptoms in conditions such as osteoarthritis and rheumatoid arthritis through enhancing movement and motion in joints. The other benefit of Boswellia is its capacity to increase collagen synthesis, which is critical in the repair and regeneration of the cartilage hence facilitating the process of arthritic conditions [25-31].

### *Zingiber officinale*

Ginger (*Zingiber officinale*) contains bioactive compound such as gingerol that have high anti-inflammatory and analgesic effects. These substances have been found to inhibit the action of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes that are involved in decreasing the synthesis of pro-inflammatory by-products like prostaglandins. Ginger has proved efficient in reducing the pain and swelling of arthritis patients due to the reduction of the amount of pro-inflammatory cytokines. Moreover, the plant has antioxidant properties, which protect the joint cartilages, thus ginger can provide support in the treatment of arthritis [32,33].

### *Tribulus terrestris*

The traditional use of *Tribulus terrestris* is synonymous to the treatment of some inflammatory diseases such as, arthritis. Its active phytochemicals, including saponin, flavonoid, and alkaloid, have anti-inflammatory and analgesic properties since they regulate inflammatory routes and lower oxidative stress. Tribulus has been shown to suppress the synthesis of inflammatory cytokines such as TNF-alpha and IL- 6 that participate in pathogenesis of arthritis. Tribulus studies have proposed it to help limit the joint soreness, rigidity, and edema by enhancing movements and lifestyle standards in arthritics [34-36].

### *Camellia sinensis*

Green tea is made out of a plant *Camellia sinensis* which has been known to have antioxidant and anti-inflammation effects. Polyphenols specially epigallocatechin gallate (EGCG) in green tea have been shown to have significant anti-arthritic activity due to their ability to prevent the pro-inflammatory cytokines and enzymes such as COX-2. EGCG also plays the role in minimizing the oxidative impairment of joint tissues and avoid deterioration of cartilage. Green tea is one of the promising natural treatment of arthritis as it has been observed to reduce pain, inflammation and damage to joints in cases of osteoarthritis and rheumatoid arthritis when regular green tea is consumed [37].

### *Withania somnifera*

An herb called *Withania somnifera* or Ashwagandha has an interesting anti-inflammatory as well as adaptogenic effect. It has been known to decrease inflammation through immunomodulatory effect and suppressing the concentrations of the cytokines that induce inflammation like TNF-alpha and IL-1-beta. The anti-oxidant property of *Withania somnifera* also has anti-arthritic properties that shields the joint tissues against oxidative arthritic destruction. Research has shown that supplementation of Ashtagandha improves general movements of joints and relieves pain, stiffness, and swelling among individuals with rheumatoid arthritis and osteoarthritis [38-40].

### *Piper longum*

Bioactive compounds in *Piper longum* or long pepper such as piperine have been found to be very potent in anti-inflammatory and analgesic activity. Piperine suppresses expression of COX-2 and inflammatory cytokines and this led to a decrease in joint pain and inflammations that were related to arthritis. Long pepper has also been proven to augment the bioavailability of other therapeutic alternatives, making it a good supplement in the treatment of arthritis. Its pain and inflammation reducing, as well as antioxidant properties have made it be used in traditional medicine in the treatment of inflammatory conditions such as arthritis [41-44].

## METHODOLOGY

The Molecular Docking study was performed using Molegro Virtual Docker version 28.2.

### Protein Preparation

The 3-D crystal structure of the targeted Anti-Arthrtic protein COX-2 (PDB ID: 5F19), The Crystal Structure of Aspirin Acetylated Human Cyclooxygenase-2 was retrieved from the Protein Data Bank (PDB) (www.rcsb.org/pdb). To analyze the structural features and active sites of these proteins, we utilized CASTP (Computed Atlas of

Surface Topography of Proteins) alongside PyMOL molecular visualization software. This approach allowed for a detailed examination of the surface properties and potential interaction sites of the proteins. Lipinski's rule of five states that compounds that are good candidates for drug development should have the following properties: a molecular weight of less than 500 g/mol, a log P partition coefficient of less than five, fewer than ten hydrogen bond acceptors (mainly N and O), no more than five hydrogen bond donors (OH and NH groups, for example), and fewer than ten rotatable bonds. These requirements are essential for guaranteeing the medication candidates' adequate oral bioavailability and pharmacokinetics. As a result, substances that satisfied these standards were chosen for docking studies, in which their affinities for binding to COX – 2 were evaluated. Through a stringent screening procedure, we hope to find promising candidates who can successfully target the defective COX – 2 proteins linked to arthritis, possibly developing new therapeutic approaches.

### Ligand Preparation

The major phytoconstituent that is present inside both the species which is responsible for anti-cancer activity is identified by the GC – MS analysis done previously by researcher's and those compound's 3D structures are retrieved using Pubchem database.

### Molecular Import and Preparation

The molecular structure files were read into meaningful parts (ligands, cofactors, water molecules and proteins) and automatically prepared. MVD was useful in identification of bonds, aromaticity, charges assignment, and explicit hydrogen addition. The inbuilt cavity detector was able to find promising sites of binding (cavities), thus being able to limit the search space to of the most intriguing areas.

### Docking

Molecular docking computer software mimics the interaction between a small molecule (ligands) and a target protein (enzyme or receptors). In this case we have involved the Molegro Virtual Docker software. MVD docking scoring function is worked out on Piecewise Linear Potential (PLP). In the case of each ligand docking the best ligand-protein complex orientation was studied and hydrogen bonds found and marked. The energy of ligands was examined and measured through the MVD score, which is a linear frame of hydrogen bonding as well as the electrostatic contacts. All valence checks and addition of H atoms were done. The docked cavities discovered through cavity detection algorithm were actually utilized by guided different evolution search algorithm to concentrate the search, to that portion, during the docking stimulation. The unlikely preparations, as well as the lack of structural information (e.g. unknown residues) represented warnings which were attended to and efforts were made to correct the errors. Reranking procedure was used with the top ranked poses in order to enhance the percentage of docking accuracy.

### Analysis

The poses returned by the docking engine were viewed using pose organizer. Pose organizer provided the ability to read docking run poses dynamically thus allowing browsing of thousands of docked ligand structures. A selection of different energy terms and interactions have been checked at once and further reranking and binding affinity values have been computed. In the inter-conversion of the poses,' electrostatic interactions and hydrogen bonding interactions were updated dynamically. Obtained MolDock score of the selected ligands was compared with the standard drug. The ligands with optimal MolDock values were termed as the most appropriate ligands and a potential lead structure against the arthritis condition [2-9].

## RESULT

MolDock is built on a new heuristic search algorithm which integrates cavity prediction and differential evolution. The docking scoring function A variation of the piecewise linear potential (PLP), the docking scoring function of MolDock includes novel hydrogen bonding and electrostatic terms. The important docking analysis parameter is called MolDock Score.

The ligand molecules were evaluated using MolDock score, rerank score and hydrogen bonds interactions. The ligand bearing minimum MolDock score has a high affinity with the target. Table 1 shows In-Silico docking analysis of the ligands selected against human Cyclooxygenase - 2.

**Table 1: Ranking of Ligands and poses against human COX – 2 based on MolDock score Protein: 5F19**

| Ligand | Species Name | MolDock Score | Rerank Score | H Bond |
|---|---|---|---|---|
| 65064 | *Camellia sinensis* (Epigallocatechin-3-gallate (EGCG)) | -148.025 | -126.423 | -19.051 |
| 168928 | *Boswellia serrata* (Boswellic acid) | -122.709 | -11.7873 | -5.31182 |
| 265237 | *Withania somnifera* (Withaferin A) | -117.477 | -35.0132 | -7.59488 |
| 638024 | *Piper longum* (Piperine) | -116.014 | -89.7546 | -3.12064 |
| 442793 | *Zingiber officinale* (6-Gingerol) | -114.165 | -69.5575 | -7.0969 |
| 5280953 | *Tribulus terrestris* (Harmine) | -98.7888 | -80.5192 | -2.49576 |
| 3033 | Standard (Diclofenac Sodium) | -94.7926 | -79.1743 | -2.53875 |

## 2D, 3D and Secondary Interaction Between Ligands and Proteins

### A. Epigallocatechin-3-gallate (EGCG) Vs 5F19

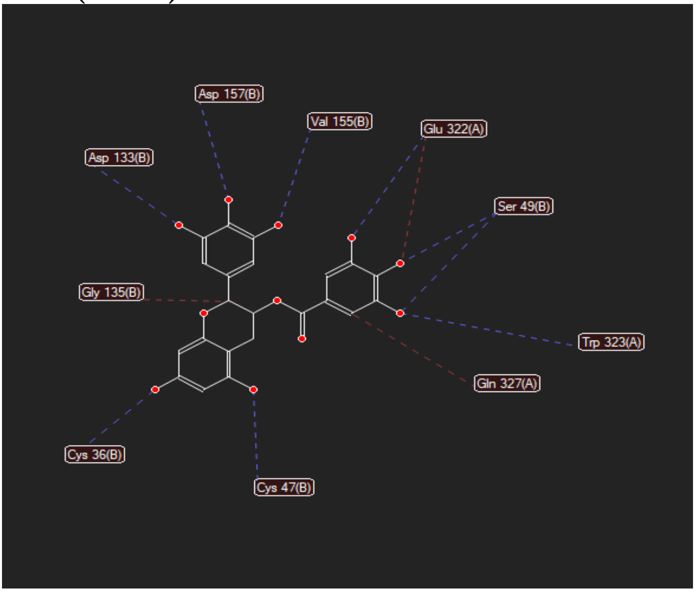

Figure 1: 2D Interaction of EGCG – 5F19

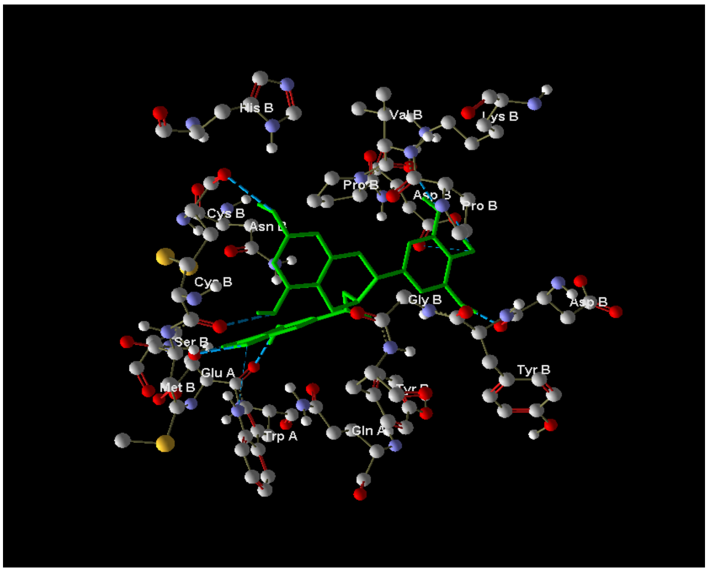

**Figure 2: 3D Interaction of EGCG – 5F19**

**Figure 3: Secondary Interaction of EGCG – 5F19**

### B. Boswellic acid Vs 5F19

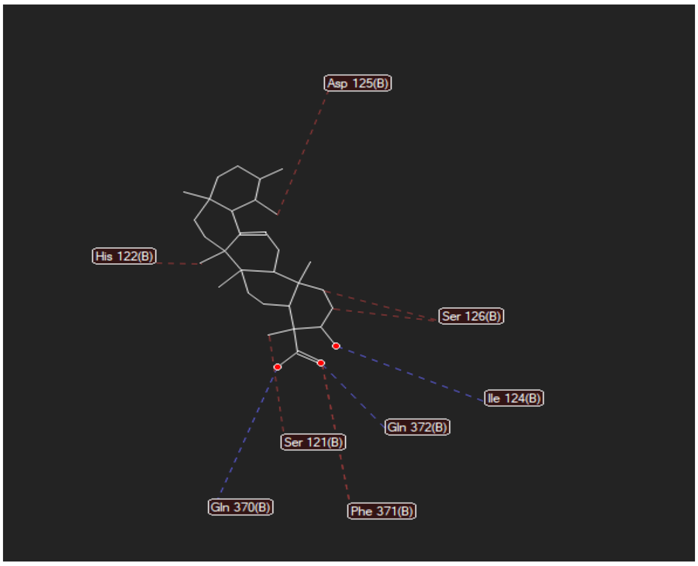

**Figure 4: 2D Interaction of Boswellic acid – 5F19**

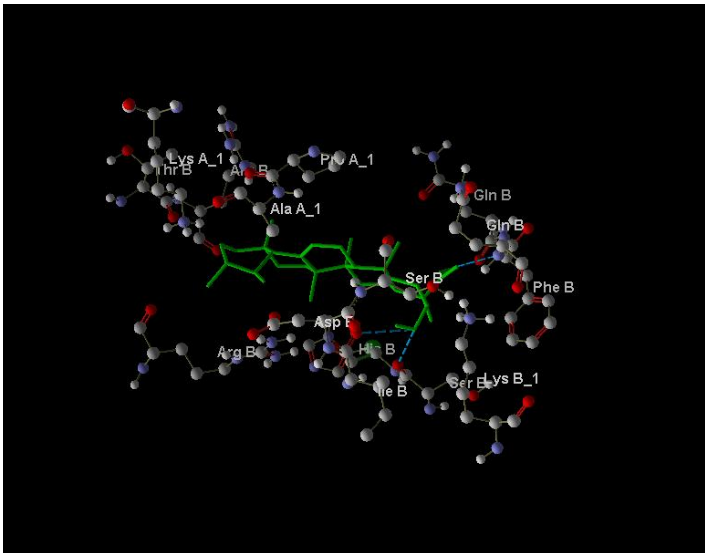

Figure 5: 3D Interaction of Boswellic acid – 5F19

Figure 6: Secondary Interaction of Boswellic acid – 5F19Withaferin A Vs 5F19

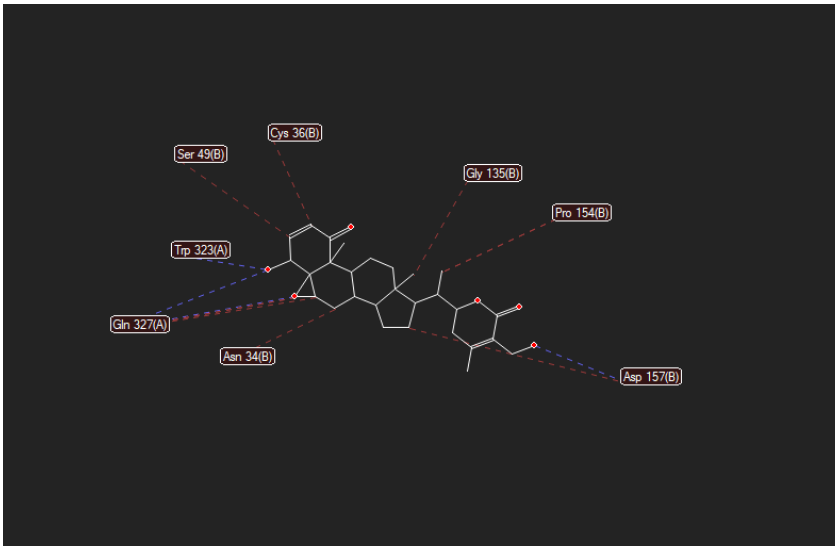

Figure 7: 2D Interaction of Withaferin A - 5F19

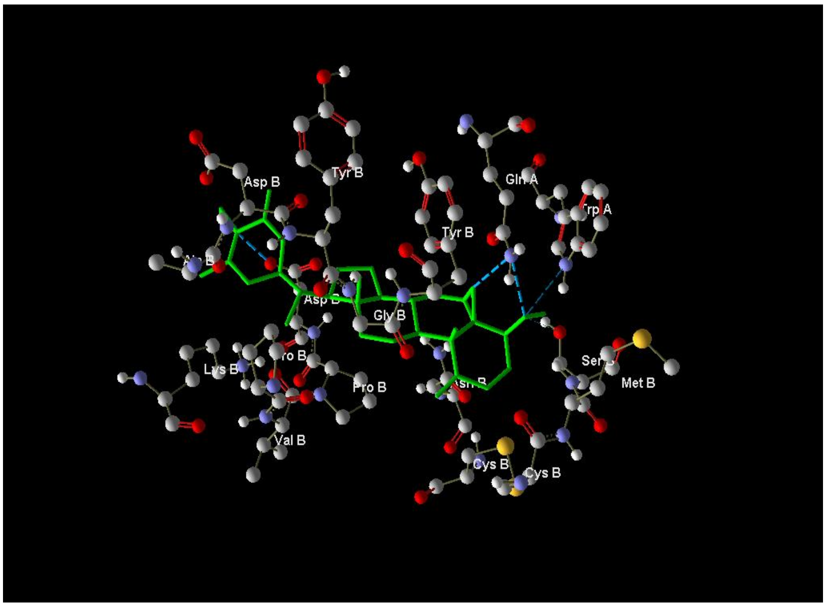

Figure 8: 3D Interaction of Withaferin A - 5F19

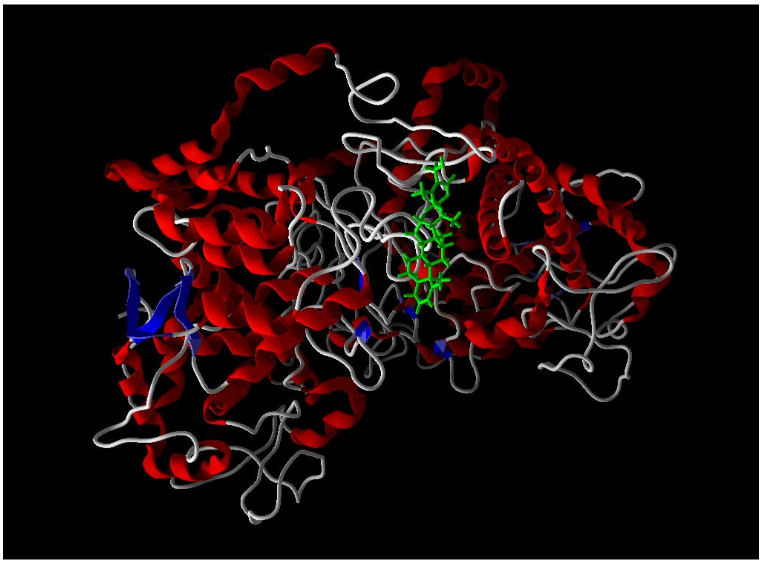

Figure 9: Secondary Interaction of Withaferin A - 5F19

## C. Piperine Vs 5F19

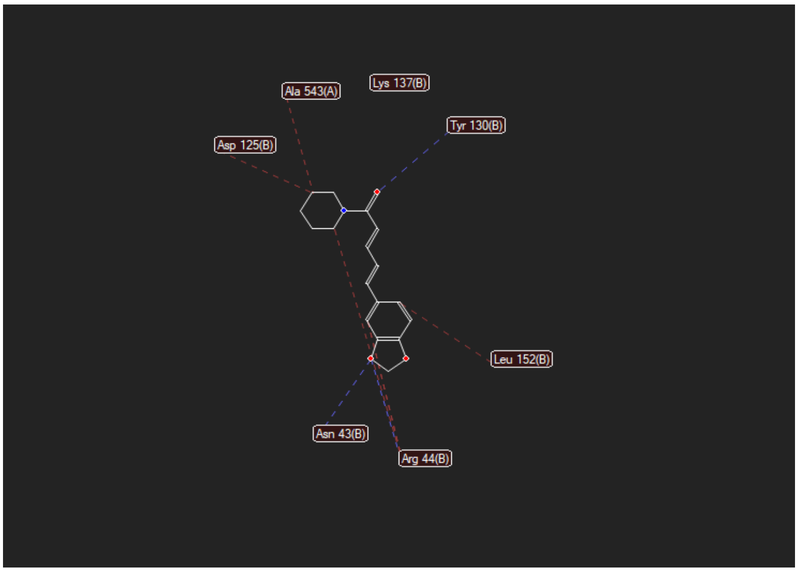

Figure 10: 2D Interaction of Piperine - 5F19

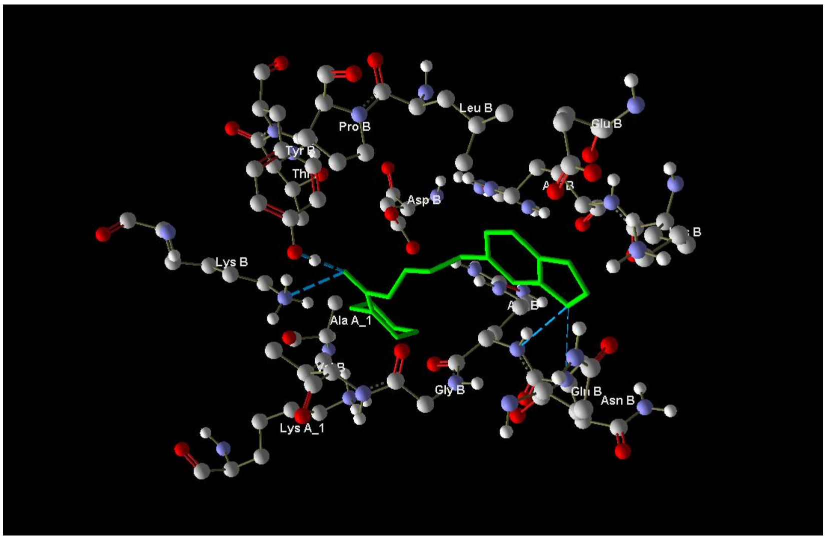

Figure 11: 3D Interaction of Piperine - 5F19

Figure 12: Secondary Interaction of Piperine - 5F19

## D. 6-Gingerol Vs 5F19

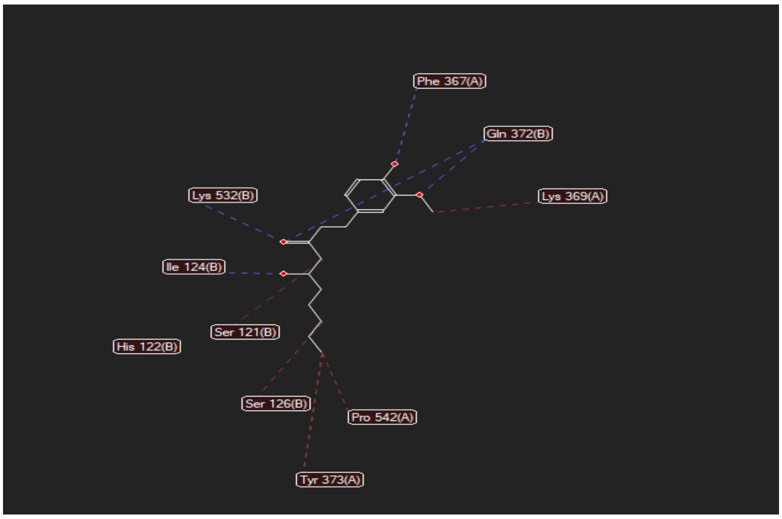

Figure 13: 2D Interaction of 6-Gingerol - 5F19

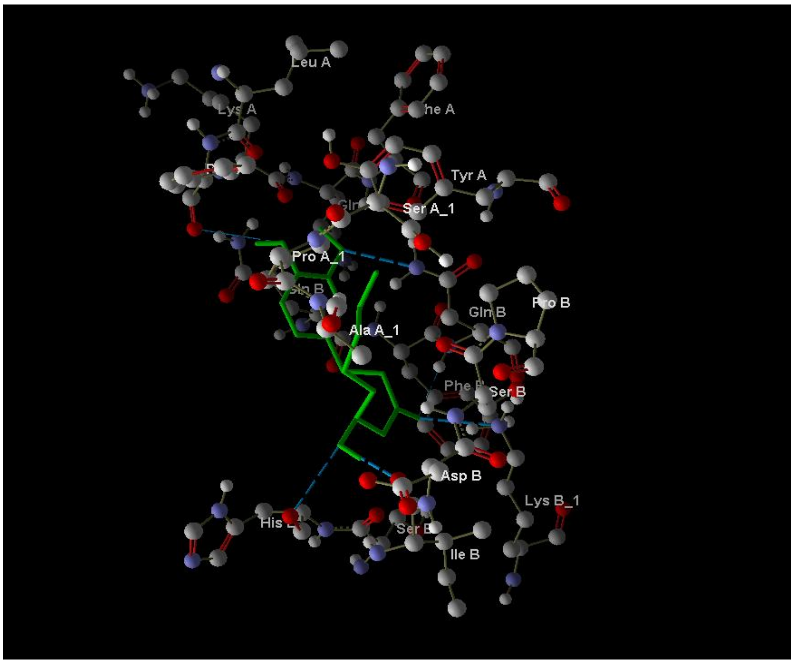

Figure 14: 3D Interaction of 6-Gingerol - 5F19

Figure 15: Secondary Interaction of 6-Gingerol - 5F19

## E. Harmine Vs 5F19

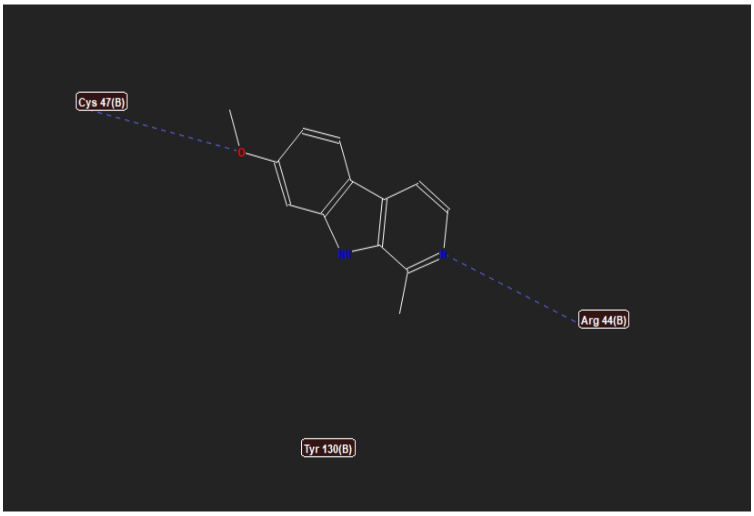

Figure 16: 2D Interaction of Harmine - 5F19

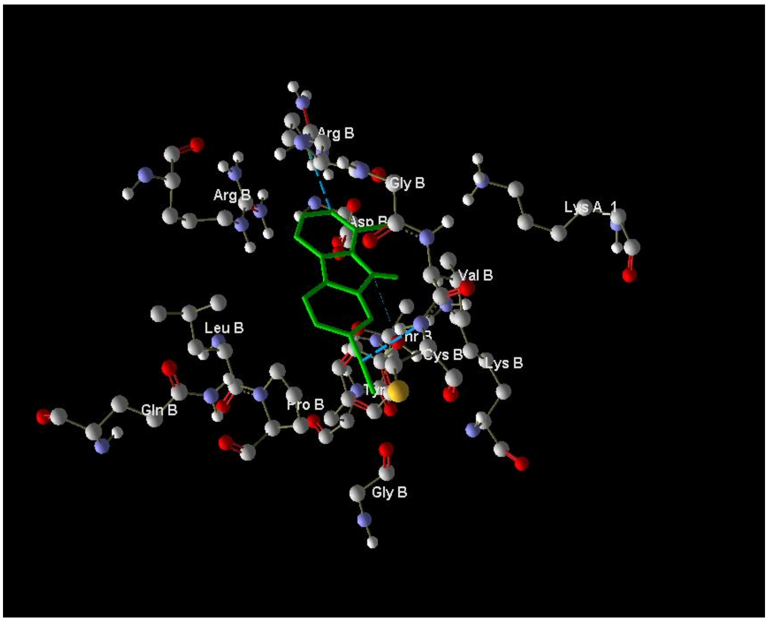

Figure 17: 3D Interaction of Harmine - 5F19

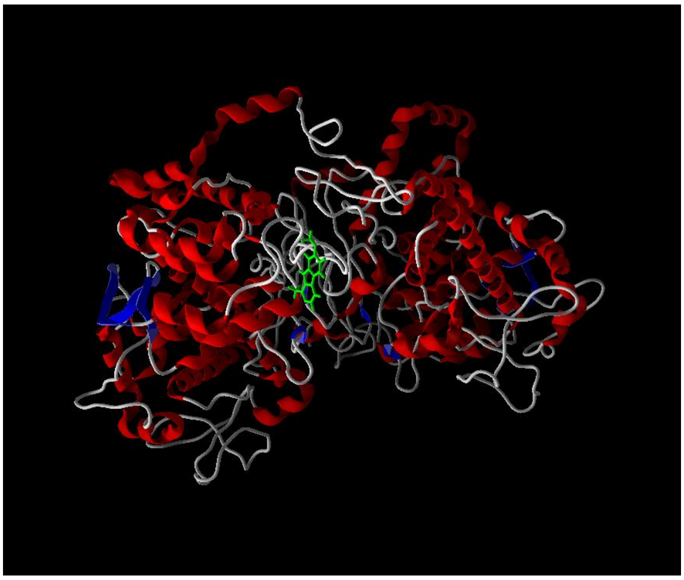

Figure 18: Secondary Interaction of Harmine - 5F19

## F. Diclofenac Vs 5F19

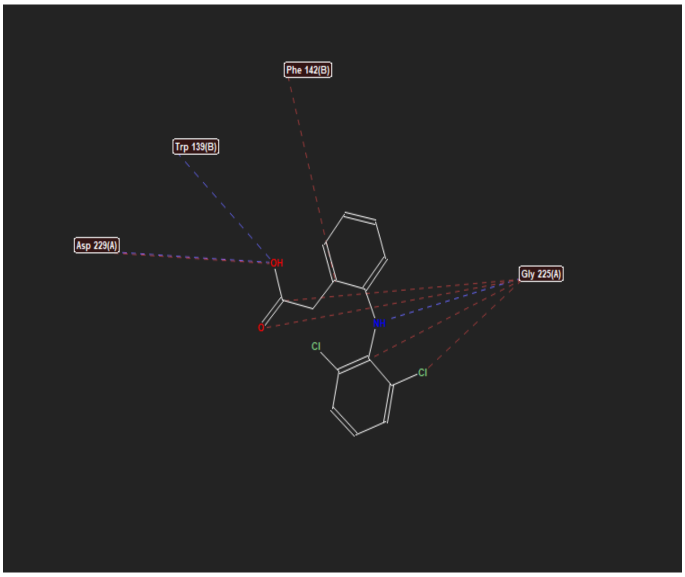

Figure 19: 2D Interaction of Diclofenac - 5F19

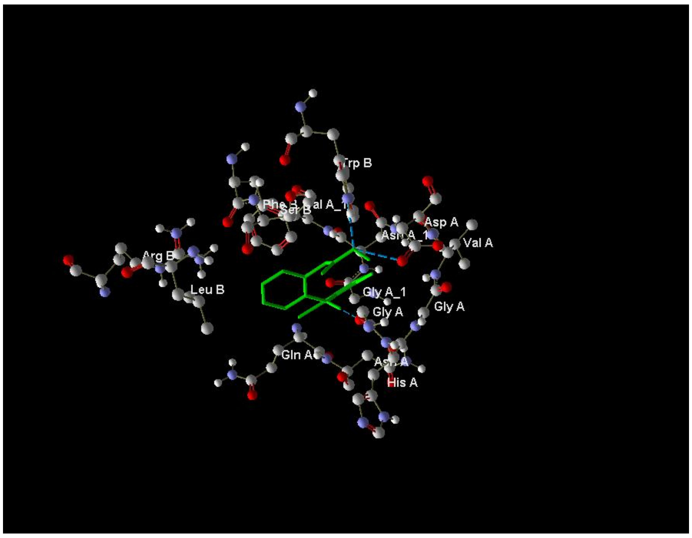

**Figure 20: 3D Interaction of Diclofenac - 5F19**

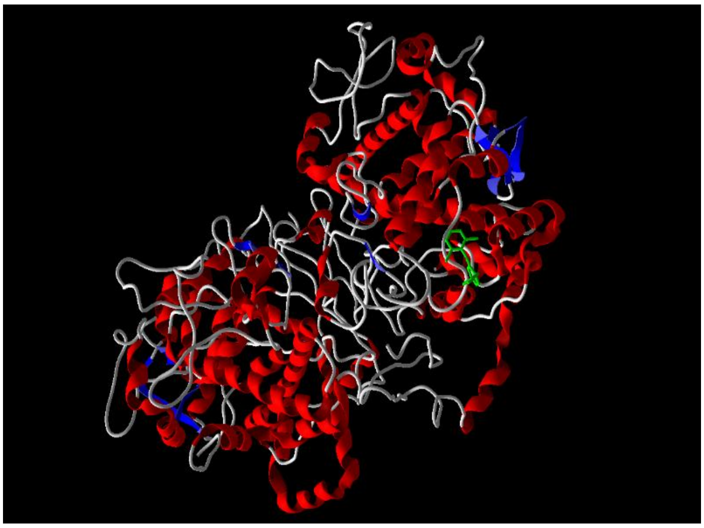

**Figure 21: Secondary Interaction of Diclofenac - 5F19**

## DISCUSSION

Rheumatoid arthritis (RA) is an autoimmune disease caused by the chronic inflammation of synovial fluid, joint pain, and successive loss of joint cartilage [1-5]. One major mediator of such an inflammatory onslaught is Cyclooxygenase-2 (COX-2) which is an induced enzyme that helps in the synthesis of the pro-inflammatory prostaglandins [6-11]. Though the non-steroidal anti-inflammatory drugs (NSAIDs) of synthetic origin like Diclofenac sodium are commonly used to treat the symptoms of RA by acting on COX-2, long-term administration is reported to cause severe side effects related to gastrointestinal tract, hepatic, renal, and cardiovascular problems [12-21]. Hence, it is necessary that safer, effective, and naturally occurring COX-2 inhibitors are sought. This work was developed through the molecular docking methods to analyze the interaction characteristics and binding potential of six phytoconstituents of popular medicinal plants with COX-2 (PDB ID: 5F19) by evaluating against Diclofenac as control standard [23-31].

### At Protein 5F19

Docking analysis showed that the Epigallocatechin-3-gallate (EGCG) of Camellia sinensis had the best binding strength (the MolDock value was -148.025), which was incredibly top when compared with that of Diclofenac sodium (MolDock value was -94.7926). EGCG also depicted highest hydrogen bond interaction energy (-19.051) that signifies stabled and voluminous binding in the active site of COX-2. The multiple hydroxyl groups on the compound as well as high polarity allows it to form multiple hydrogen bonding, which augments its inhibitory capabilities. This evidence agrees with earlier results that report on EGCG anti-inflammatory effects and postulate that COX-2 inhibition is the mechanism of action behind its therapeutic value in RA and other inflammatory diseases.

Boswellic acid of Boswellia serrata showed similar results with EGCG of having a high docking score (-122.709), in line with its long-standing traditional claim of using it in inflammatory disorders. Boswellic acid is also known to inhibit COX-2 and 5-LOX expression with a double defense of pro-inflammatory pathway. On the same tune, withaferin A, a derivative of withania somnifera had a MolDock score of -117.477 and H hydrogen a battery of -7.59488, which are signs of an assured binding to cox-2. Withaferin A is an immunomodulatory and anti-inflammatory steroidal lactone and as such appears to be a viable candidate to treat RA. The compounds exhibited similar or better interaction profiles than the standard drug and justifies their potential as natural COX-2 inhibitors.

Other phytoconstituent compounds such as Piperine of Piper longum and 6-Gingerol of Zingiber officinale have docking score of -116.014 and -114.165 respectively which means moderate. Although they are comparatively less complexed in terms of their molecular structure, both these compounds also bound significantly as compared to Diclofenac, highly indicative of potential clinical significance. They have also been well documented in terms of their anti-inflammatory activities in preclinical and clinical trials further supporting the choice of their use in the present study. A Tribulus terrestris phytoconstituent, harmine, an indole alkaloid, had the lowest docking score (-98.7888) of the phytoconstituents and had a similar amount of hydrogen bonding to Diclofenac, this indicates that harmine might have some inhibitory capacity although slight.

Use of Diclofenac sodium as a reference molecule was very useful in finding out the efficacy of the phytoconstituents. The lowest MolDock score of all test compounds underlines the potential of natural ligands as COX-2 inhibitors which could be at least as effective as chemical ones. The findings match the classical and ethnopharmacological experience of anti-inflammatory application of these herbs and give scientific support to their mechanisms of action.

To summarise, this research work affirms the usefulness of *In-Silico* docking as an intermediate in successful drug discovery pipeline. The compounds such as EGCG, Boswellic acid and Withaferin A were reported to have high binding affinity, strong hydrogen bonds and acceptable interaction patterns and therefore can be considered as potential candidates of future study. These phytochemicals need to be tested in vitro enzymatic test and in vivo animal models to enable the confirmation of their effectiveness, safety and their pharmacokinetic properties. They may also have the potential to develop them into COX-2-selective herbal therapeutics that may prove to be highly effective as well as free of all side-effects for the conventional NSAIDS in the treatment of the rheumatoid arthritis and other inflammatory disorders.

## CONCLUSION

This *In-Silico* docking investigation was able to determine a number of phytoconstituents especially EGCG, Boswellic acid, and Withaferin A as potential natural COX-2 inhibitor during Rheumatoid arthritis management. Such compounds demonstrated to be of higher strength of binding and interaction with COX-2 active site as opposed Diclofenac sodium. Because of the natural initial source and biological activity, such compounds deserve to be studied in the laboratory with the in vitro and in vivo models to confirm their effectiveness of anti-inflammatory and anti-arthritic properties. This helps the research to emphasize on the importance of herbal-derived molecules in developing safer and more effective therapeutic molecules in diseases such as chronic inflammatory disorders, such as RA.

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